Chemical Environmental Agents and the Endocrine System and Age at Puberty

Pre-and post-natal exposure to **endocrine-active environmental agents** can alter **age at onset, duration, and completion of puberty**.

General Information	
Broad Focus Area	Obesity and growth; fertility and early pregnancy; early origins of adult health.
Background and Justification	Over the last century, secular trends of decreasing age at menarche in girls has been reported in Europeans, North Americans and Australians. More recent data suggest decreasing age for both menarche and onset of breast development in the U.S.[1,2] although some critics disagree.[3,4] Theories include these changes resulting from better (and over) nutrition, greater and earlier growth, and environmental or socioeconomic factors. Recent studies of exposure to some environmental agents suggest that they may accelerate[5,6] or delay[7-9] pubertal development in girls. Few data are available to examine age at puberty in boys;[7] but laboratory data suggest that such alterations are possible.[10-11] It has recently been suggested that the effects of defined environmental hormonally-active substances on the human reproductive system and on pubertal development are biologically plausible, although differentiation is needed between the initiation of secondary sexual characteristics (peripheral puberty) and central puberty (true puberty: spermatogenesis, folliculogenesis) when assessing pubertal development.[12] A variety of hormonally-active environmental chemicals have been cited in the literature as potential endocrine disruptors, including insecticides and herbicides (e.g., DDT, atrazine); pharmaceuticals (drug estrogens); chemicals associated with consumer goods/household products (e.g., bisphenol A, phthalates, nonylphenol, polybrominated diphenyl ethers (PBDEs), perfluorooctane sulfonate (PFOS)); industrial chemicals (e.g., polychlorinated biphenyls (PCBs), dioxins, polycyclic aromatic hydrocarbons (PAHs)); heavy metals (e.g., arsenic, lead, mercury, and cadmium); and natural hormones such as the phytoestrogens. Environmental agents identified for examination in the NCS are 1) widely used or are common exposures, or 2) endocrine active compounds, some with evidence of associated alterations in timing of puberty in cross-sectional studies of humans, or in laboratory animals.[8-10, 13-17] Limited data, however, are available on specific critical windows for chemical exposures in relation to altered pubertal development, especially for low-level continuous exposures like lead and PCBs. The number of factors that can impact puberty is high and the entire prepuberal period, including in utero growth and development, should be considered as a critical period.
Prevalence/ Incidence	According to the CDC (2003),[18] the average age of puberty for girls is between the ages of 8 and 13, and the average age of puberty for boys is between the ages of 9

	and 14. It is estimated that approximately 37% of 7-year-old and 52% of 8-year-old African-American girls showed signs of precocious puberty, while corresponding numbers for Caucasian girls were 6% and 16%, respectively.[1] Exposure to hormonally active agents (HAAs) in the residential environment can occur from a variety of sources, such as via contaminated drinking water, polluted air, ingesting food, and contacting or ingesting contaminated soil or dust, as well as through the use of certain commercial products containing synthetic HAAs (e.g., cleaners, pesticides, cosmetics and food additives).[28] Rudel et al. (2003) investigated potential indoor exposures to numerous endocrine disruptors found in consumer uses.[29] Results of analyses of indoor air and dust from 120 homes for 89 organic chemicals identified as potential endocrine disruptors showed that fifty-two of the compounds were present in air, with the most abundant compounds in air including phthalates (plasticizers, emulsifiers), o-phenylphenol (disinfectant), 4-nonylphenol (detergent metabolite), and 4-tert-butylphenol (adhesive). Sixty-six endocrine disrupting compounds were present in dust samples taken from homes, with frequent detections of penta- and tetrabrominated diphenyl ethers (flame retardants) and numerous pesticides in dust. An intermediate of a flame retardant banned in 1977 (2,3-dibromo-1-propanol), as well as the banned pesticides heptachlor, chlordane, methoxychlor, and DDT, were also frequently detected in dust and air, suggesting limited indoor degradation over time.[29] According to the authors, for 15 compounds detected concentrations exceeded government health-based guidelines, but no guidelines are available for 28 compounds, and existing guidelines do not consider endocrine effects.
Economic Impact	Very early or very late puberty has been associated with a number of conditions, potentially during adolescence, and more likely during adulthood, that come with increased health care costs. Early menarche is reported to be a risk factor for breast cancer, underscoring the role of early developmental milestones as indicators for adult onset disease.[19] Certain girls with premature adrenarche are at risk of developing functional ovarian hyperandrogenism, polycystic ovarian syndrome, and hyperinsulinism).[20, 21] Psychological and psychosocial disturbances are also associated with precocious puberty; Central precocious puberty often leads to lower self-esteem, and early menarche has been associated with comorbid depression and substance abuse.[22] Delayed puberty can result in short stature and lack of sexual development, characteristics which may lead to emotional and social difficulties. Bone mass gain is rapid during puberty, and recent data suggest that a delay in pubertal maturation may cause prolonged, possibly irreversible defects in bone mineralization, thus altering peak bone mass and interfering with the normal bone accretion process, later causing osteoporosis.[23, 24]

Exposure Measures		Outcome Measures

Primary/ Maternal	Bisphenol A; Atrazine; Lead; Dioxins; PCBs		***Primary/ Child***	Tanner stage exam and physical-anthropometric measures (male and female); Menstrual history (female); Spermarchy (male)
Methods	Blood sample; Urine sample; Breast milk sample		Methods	Urine samples; Interview; Physical exam (or self exam);
Life Stage	Preconception, prenatal & throughout nursing		Life Stage	Yearly, starting at ages 6 for girls and 7 for boys until age 18
Primary/ Child	Bisphenol A; Atrazine; Lead; Dioxins; PCBs		***Secondary/ Child***	
Methods	Blood sample; Urine sample		Methods	
Life Stage	Birth & throughout nursing, through adolescence.		Life Stage	

Important Confounders/Covariates	
Obestiy; Diet and nutrition measures	Higher percentage of body fat increases the risk of precocious puberty; later onset in underdeveloped nations is often attributed to poor nutrition.[25]
Smoking status of parents; Urine cotinine	Smoking, pre and postnatal, may reduce the age of onset of puberty.[26] Urine cotinine is measured to examine active/passive smoking exposures.
Mother's menstrual and reproductive history	Generally, the mother's menstrual history is considered the biggest predictor of age of puberty. Some of this effect may be seen in ethnic differences.[25]
Gestational age at birth	There is some evidence that a younger gestational age at birth is a predictor of earlier age at menarche; however, evidence points to small for gestational age (SGA) as the predictor of precocious puberty.[27]
Mother's alcohol consumption during pregnancy	Some studies have reported later onset of puberty due to maternal alcohol use; other recent studies have found no effect.[25]
SES and Stress	The impact of stressful sociologic factors has been related to precocious pubertal development.
Certain diseases or conditions	Precocious puberty has been associated with conditions such as neurofibromatosis, hypothyroidism, polycystic ovary syndrome, etc; Delayed puberty has been associated with conditions such as sickle cell disease, thalassaemia, Celiac disease, Gaucher disease type 1, Cushing's disease, and other endocrine deficiencies.

Population of Interest		**Estimated Effect that is Detectable**
All pregnant women and their offspring. Puberty timing, progression and completion would be examined in both girls and boys. Subgroups of special interest include: those in		Sample size estimates based on existing methods for monitoring puberty and information about the timing of puberty available in the literature generally range between 5000 and 20,000 children. These were based on estimates

rural communities exposed chronically or seasonally to pesticides; African-American girls (who usually demonstrate an earlier entrance into puberty than other races, implying unique genetic and/or environmental factors); children with certain diseases or conditions (For precocious puberty - neurofibromatosis, hypothyroidism, polycystic ovary syndrome, etc; delayed puberty - sickle cell disease, thalassaemia, Celiac disease, Gaucher disease type 1, Cushing's disease, etc.); populations consuming foods such as fish with high concentrations of bioaccumulative endocrine active chemicals.		of exposure to relatively high levels of chemicals of concern set at 10 or 20% of the study population. Refinements in current methods for assessing puberty (e.g., by developing more objective and sensitive indicators, including biochemical and molecular biomarkers) would be expected to improve the power.

Other Design Issues	
Ethical/Burden Considerations	1. The study will need to have a formal strategy and process for an effective communication of the results of physiological and biochemical measures to the child's parents and to a responsible health care provider. Any abnormalities identified in blood or anthropometric measurements would be noted and appropriate follow-up medical care recommended. 2. The study also will also need to have a formal strategy and process for effective communication of the results of environmental monitoring to the child's parents along with appropriate and feasible recommendations regarding the correction of any unhealthful environmental findings. 3. Potential embarrassment about pubertal issues. 4. The influence of DNA collection for genetic evaluation and RNA for gene expression profiling presents ethical questions. 5. Some minimally invasive procedures possible. 6. Repeated tests are potentially burdensome
Cost/Complexity of Data Collection	It will be important to have good retention rates to allow examination of pubertal progression and completion.

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